

A “Hot” Topic in Dyslipidemia Management—“How to Beat a Flush”: Optimizing Niacin Tolerability to Promote Long-term Treatment Adherence and Coronary Disease Prevention

TERRY A. JACOBSON, MD

Niacin is the most effective lipid-modifying agent for raising high-density lipoprotein cholesterol levels, but it also causes cutaneous vasodilation with flushing. To determine the frequency of flushing in clinical trials, as well as to delineate counseling and treatment approaches to prevent or manage flushing, a MEDLINE search was conducted of English-language literature from January 1, 1985, through April 7, 2009. This search used the title keywords *niacin* or *nicotinic acid* crossed with the Medical Subject Headings *adverse effects* and *human*. Niacin flushing is a receptor-mediated, mainly prostaglandin D₂-driven phenomenon, the frequency, onset, and duration of which are largely determined by the distinct pharmacological and metabolic profiles of different niacin formulations. Subjective assessments include ratings of redness, warmth, itching, and tingling. In clinical trials, most (>60%) niacin users experienced mild or moderate flushing, which tended to decrease in frequency and severity with continued niacin treatment, even with advancing doses. Approximately 5% to 20% of patients discontinued treatment because of flushing. Flushing may be minimized by taking niacin with meals (or at bedtime with a low-fat snack), avoiding exacerbating factors (alcohol or hot beverages), and taking 325 mg of aspirin 30 minutes before niacin dosing. The current review advocates an initially slow niacin dose escalation from 0.5 to 1.0 g/d during 8 weeks and then from 1.0 to 2.0 g in a single titration step (if tolerated). Through effective counseling, treatment prophylaxis with aspirin, and careful dose escalation, adherence to niacin treatment can be improved significantly. Wider implementation of these measures should enable higher proportions of patients to reach sufficient niacin doses over time to prevent cardiovascular events.

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GPR = G_i protein-coupled receptor; HDL-C = high-density lipoprotein cholesterol; NSAID = nonsteroidal anti-inflammatory drug; PG = prostaglandin; RCT = randomized controlled trial

Reducing low-density lipoprotein cholesterol levels is the primary treatment for preventing cardiovascular disease, largely because of robust evidence from randomized controlled trials (RCTs) involving statins.^{1,2} However, many patients optimally treated with statins have residual cardiovascular risk³ associated with low levels of high-density lipoprotein cholesterol (HDL-C), elevated levels of triglycerides, and a preponderance of small, dense (atherogenic) low-density lipoprotein particles.

Niacin (3-pyridine-carboxylic acid; C₆H₅N₂O₂) is the most effective medication to raise HDL-C levels. A water-soluble B-complex (B₃) vitamin used to treat pellagra, niacin was discovered to lower cholesterol levels at higher (gram) doses in 1955.⁴ It was also the first lipid-lowering therapy proven in RCTs to significantly lower (by 27%) the risk of myocardial infarction and the risk of all-cause

mortality in the long term (by 11%),^{5,6} as well as confer significant angiographic benefits (Table 1).^{7,10-15}

Niacin improves the entire lipid panel in patients with dyslipidemia, lowering apolipoprotein B-containing lipoproteins and raising apolipoprotein A-containing lipoproteins (eg, high-density lipoproteins).¹⁶ Putative mechanisms for these multidimensional lipid benefits involve interactions of niacin with its G_i protein-coupled receptor (GPR109A) in adipose tissue, reducing free fatty acid release.^{17,18}

One potential obstacle to effective use of lipid therapies is suboptimal treatment adherence and long-term persistence.¹⁹⁻²⁷ In recent studies, approximately 53% of niacin users did not reach recommended daily maintenance doses of 1.0 g or higher, 92% did not reach doses of 2 g, and flushing severity significantly predicted niacin treatment discontinuation.^{28,29} This systematic review (1) explores the pathophysiology of niacin flushing, (2) characterizes its typical clinical presentation, (3) assesses the approximate frequency of niacin flushing and of discontinuations ascribed to flushing in clinical trials, (4) explores potential strategies to prevent or minimize flushing, and (5) surveys ongoing controversies.

METHODS

An English-language MEDLINE search dating from January 1, 1985 (the year of a key active-comparator trial of immediate- and sustained-release niacin³⁰), to April 7, 2009 (date of searches), was performed. This search used the title keyword *niacin* or *nicotinic acid* crossed (using the Boolean operator “AND”) with the Medical Subject Heading *adverse effects* and the Medical Subject Heading term *human*, also joined by the Boolean operator “AND.” These sets were crossed with the publication types of correspondence, case reports and series, and comments/editorials

From the Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University School of Medicine, Atlanta, GA.

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Address reprint requests and correspondence to Terry A. Jacobson, MD, Director, Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University, Faculty Office Building, 49 Jessie Hill Jr Dr SE, Atlanta, GA 30303 (tjaco02@emory.edu).

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TABLE 1. Efficacy and Tolerability Findings From Major Randomized Controlled Trials of Niacin-Containing Therapies^a

| Reference ^b | Population/ follow-up (y) | Treatment (No. of patients randomized) | Change from baseline in lipid levels with active treatment (%) | Change from baseline in clinical/angiographic/imaging end points with niacin vs placebo or other comparator (%) | Niacin vs placebo or other comparator (%) | | |
|-----------------------------------|---|--|--|---|---|----------------------|--|
| | | | | | Frequency of flushing (ever) | Discon- tinuation | Adherence |
| CDP ^{5,6} | Men 30-64 y after MI/5-15 | IR niacin, 3.0 g (1119); placebo (2789) | TC: -10 TG: -19 | Nonfatal MI (5 y): -27 (<i>P</i> <.05); total mortality (15 y): -11 (<i>P</i> <.001) | 92 vs 4 (<i>P</i> <.05) | NA | 66 vs 78 |
| CLAS ^{7,8} | Men 40-59 y after CABG/ 2-4 | IR niacin, 3.0-12.0 g (mean, 4.3), and BAR (80); placebo (82) | TG: -22 LDL-C: -43 HDL-C: +37 | Atherosclerotic regression: IR niacin: 16; placebo: 2 (<i>P</i> =.002) | 91 vs 6 (<i>P</i> <.01) | NA | NA |
| FATS ⁹ | Men ≤62 y with high ApoB and CHD/2.5 | IR niacin, 0.25-6.0 g, and BAR, 15-30 g (36); placebo and BAR (46) | TG: -29 LDL-C: -32 HDL-C: +43 | Atherosclerotic regression: IR niacin and BAR: 39 vs placebo: 11 (<i>P</i> <.005) Clinical events ^c : IR niacin and BAR: -78 (<i>P</i> <.01) vs placebo/BAR at end point | NA | NA | 86 IR niacin and BAR vs 89 placebo and BAR |
| HATS ¹⁰ | <70 y with CHD, low HDL-C levels, and ≥3 coronary arteries with ≥30% stenosis/3 | SR niacin, 0.5-2.0 g (with increase in IR niacin to 3-4 g if increase in HDL-C is inadequate [mean, 2.4 g]) and simvastatin (+0.1 g of niacin) (33); placebo (34) | TG: -36; LDL-C: -42 HDL-C: +26 | Atherosclerotic regression with niacin: 0.4 vs athero- sclerotic progression with placebo: 3.9 (<i>P</i> <.001) Clinical events ^d : 3 vs 32 (-81%; <i>P</i> =.03) | 30 vs 23 (<i>P</i> =.35) | 3 | 80 SR niacin and simvastatin vs 80 placebo |
| ARBITER 2 ^{11,15} | >30 y with CHD and low HDL-C levels while taking statin | ER niacin, 0.5-1.0 g, and statin (87); placebo and statin (80) | TG: -13 LDL-C: -2 HDL-C: +21 | CIMT progression: -0.004 mm vs +0.044 mm in euglycemic patients (<i>P</i> =.026) | 69 vs 13 (<i>P</i> <.001) | NA | 90-95 (<i>P</i> =NS vs placebo) |
| AFREGS ¹² | <76 y with CHD and low HDL-C levels/2.5 | GF, 1.2 g; IR niacin, 0.25-3 g; and BAR, 16 g (71); placebo and TLC (72) | TG: -46 LDL-C: -22 HDL-C: +38 | % Stenosis: -0.8 vs +1.4 (<i>P</i> <.05) Clinical events ^e : 13 vs 26 (<i>P</i> =.04) | 92 vs 25 (<i>P</i> <.001) | 10 vs 3 | 87-90 vs 88-92 |
| ARBITER 6- HALTS ¹³ | Atherosclerotic CHD or vascular disease, CHD risk equivalent or 10-y Framingham absolute CHD risk ≥20%, and LDL-C ≥100 mg/dL and HDL-C <50 mg/dL (men) or <55 mg/dL (women)/1.2; 14 mo | ER niacin, 2.0 g (target or MDT) (97) or EZ, 10 mg (111), plus ongoing statin at stable dose | ER niacin/statin LDL-C: -12.4 HDL-C: +17.6 EZ/statin LDL-C: -21.0 HDL-C: -6.5 (<i>P</i> ≤.01 for each between-group comparison) | Imaging ER niacin/statin: -0.0142 mm in CIMT at 14 mo EZ/statin: -0.0007 mm (<i>P</i> =.01) Clinical events ER niacin/statin: 1% incidence of MACE at 14 mo EZ/statin: 5% incidence (<i>P</i> =.04) | 36 vs NA | 15 vs 9 | 88 vs 95 |

^a AFREGS = Armed Forces Regression Study; ApoB = apolipoprotein B; ARBITER = Arterial Biology for the Investigation of Reducing Cholesterol; BAR = bile acid resin (sequestant); CABG = coronary artery bypass graft; CDP = Coronary Drug Project; CHD = coronary heart disease; CIMT = carotid intima-media thickness; CLAS = Cholesterol-Lowering Atherosclerosis Study; ER = extended-release; FATS = Familial Atherosclerosis Treatment Study; GF = gemfibrozil; HALTS = HDL and LDL Treatment Strategies; HATS = HDL Atherosclerosis Treatment Study; HDL-C = high-density lipoprotein cholesterol; IR = immediate-release; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MDT = maximum dose tolerated; MI = myocardial infarction; NA = not available; NS = not significant; SR = sustained-release; TC = total cholesterol; TG = triglyceride; TLC = therapeutic lifestyle counseling.

^b Study reports presented in ascending order of date published for major clinical trials reporting data on both efficacy and tolerability or adherence. Comparisons denote active treatment vs placebo, usual care, or statin monotherapy, except where noted.

^c Death, MI, revascularization, or worsening ischemia.

^d Cardiovascular death, MI, revascularization, ischemia.

^e Death, MI, hospitalization for angina pectoris, stroke or transient ischemic attack, or revascularization.

using the operator “NOT,” thereby excluding these types of publications. Also excluded using “NOT” were articles related to *smoking* (NOT: title keyword *nicotin**, *smok**, *cigar**) or *schizo** (the normal flushing response is blunted in many patients with schizophrenia). This search returned 205 citations, of which 56 are included in this review. Many of the remaining articles, including reviews and meta-analyses,

were subjected to “saturation searches,” which produced additional articles of interest. Other articles were known to the author or identified by using title keywords, including *flush**, *vaso**, *cutan**, *prostagl**, *Niasp**, and *larop**. Other sources of data included full US-prescribing information for niacin-containing treatments and online reports from regulatory agencies.

OVERVIEW OF NIACIN FORMULATIONS

The earliest form of niacin was immediate-release niacin, which is also termed *plain* or *crystalline* niacin. Some formulations are available as dietary supplements, whereas others have Food and Drug Administration–approved labeling as lipid-modifying therapies (Niacor; Upsher-Smith, Minneapolis, MN; Nicolar, sanofi-aventis, Bridgewater, NJ).¹¹ Early attempts to reformulate niacin largely to limit flushing resulted in sustained-release niacin, which releases niacin more slowly via combination with an inert (resinous) base.¹¹ Examples include Slo-Niacin (Upsher-Smith) and Nicobid (sanofi-aventis). Endurance Products Company (Tigard, OR) manufactures niacin formulated in a wax matrix (ENDUR-ACIN). Finally, inositol hexanicotinate (Niacinol; Integrative Therapeutics, Green Bay, WI) is a synthetic prodrug that consists of 6 molecules of niacin esterified to 1 molecule of inositol. Often advertised as “flush-free” niacin, it also appears to be “effect-free” because the esterified niacin is not bioavailable.³¹

Food and Drug Administration–approved, prescription niacin-containing treatments include extended-release niacin (Niaspan; Abbott Pharmaceuticals, Abbott Park, IL), extended-release niacin and lovastatin (Advicor; Abbott Pharmaceuticals), and extended-release niacin and simvastatin (Simcor; Abbott Pharmaceuticals).³²⁻³⁴ Although the terms *extended-release*, *sustained-release*, *slow-release*, *controlled-release*, *long-acting*, and *timed-release* niacin all denote different forms of extended-release niacin products, for the purposes of this review, the term *extended-release niacin* is used only for references specifying any of these terms (or Niaspan, Advicor, or Simcor).

OVERVIEW OF PATHOPHYSIOLOGY OF NIACIN FLUSHING AND PHYSIOLOGY OF TOLERANCE

Interactions between niacin and GPR109A receptors on epidermal Langerhans cells result in increased cytosolic calcium; this increase triggers increases in phospholipase A₂ activity and expression of prostaglandin (PG) D₂ synthase, with elevated mobilization of arachidonic acid into vasodilator eicosanoids and prostanoids.³⁵⁻³⁷ Lipid-lowering doses of niacin are associated with 430- to 800-fold increases in circulating levels of a stable PGD₂ metabolite (9- α -11- β -PGF₂).³⁸ PGD₂ binds to DP1 receptors on local capillary smooth muscle cells,^{37,39} causing capillary vasodilation in the papillae of the upper dermis.⁴⁰ Acetylsalicylic acid (aspirin) and nonsteroidal anti-inflammatory drugs (NSAIDs) can prevent or blunt flushing by blocking PGD₂ synthesis via cyclooxygenase (chiefly, cyclooxygenase 1). However, other PGs (eg, PGE₁), other mediators (eg, serotonin), and other signaling pathways may also be involved.

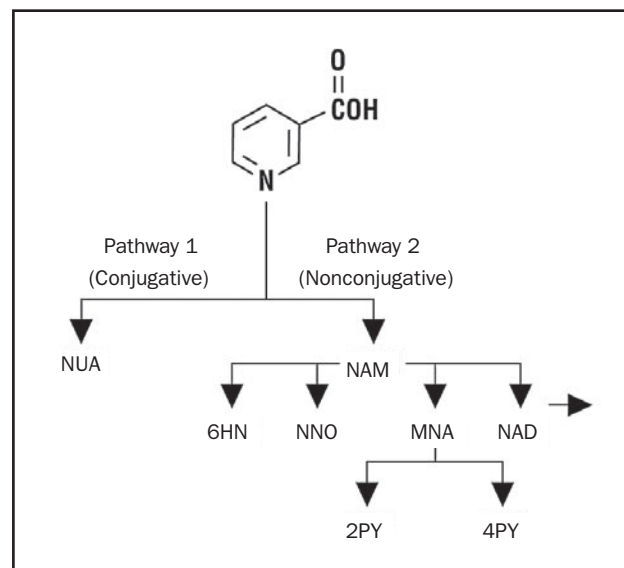


FIGURE 1. Niacin metabolism. Niacin is metabolized via 2 pathways. In the first low-affinity, high-capacity pathway (pathway 1, left), niacin is conjugated with glycine to form nicotinuric acid (NUA). The second high-affinity, low-capacity pathway (pathway 2, right) involves a number of oxidation-reduction reactions that produce nicotinamide (NAM) and ultimately pyrimidine metabolites. 6HN = 6-hydroxy-nicotinamide; COOH = carboxylic acid; MNA = N-methylnicotinamide; N = nitrogen; NAD = nicotinamide adenine dinucleotide; NNO = nicotinamide-N-oxide; 2PY = N-methyl-2-pyridone-5-carboxamide; 4PY = N-methyl-4-pyridone-5-carboxamide.

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(An elaborate consideration of mechanism exceeds the scope of this review, which is clinically focused and hence includes only human studies.)

NIACIN ABSORPTION KINETICS AND THE RISK OF FLUSHING

The pharmacodynamic effects of niacin are linked to its hepatic metabolism via 1 of 2 saturable pathways^{41,42} (Figure 1): a low-affinity, high-capacity pathway, in which niacin is conjugated with glycine to form nicotinuric acid, and a high-affinity, low-capacity amidative pathway, in which niacin forms nicotinamide. It was once thought that the conjugative pathway, and particularly formation of nicotinuric acid, was associated with flushing and that the amidation pathway, and particularly formation of nicotinamide, was associated with hepatotoxicity; the metabolic fates of niacin formulations via either of these pathways are in turn influenced by these formulations' dissolution and pharmacokinetic profiles. However, a more recent consideration of the evidence by Stern⁴³ emphasized that the parent compound nicotinic acid, through its interaction with the GPR109A receptor, is the chief mediator of flushing and not any particular metabolite, such as nicotinuric acid,

formed via the conjugative pathway. This review also concluded that “unlike flushing, the mechanism of nicotinic acid hepatotoxicity has not been determined. Specifically, there is no evidence that a metabolite is responsible. . . .”⁴³

Because immediate-release niacin is completely absorbed from the gastrointestinal tract in 1 to 2 hours, immediate-release niacin rapidly saturates the low-capacity amidation pathway, such that most of the drug is metabolized via the conjugative pathway.¹¹ The dissolution and gastrointestinal absorption of sustained-release niacin are not complete until after more than 12 hours. Sustained-release niacin is chiefly metabolized by the amidation pathway and has been associated with hepatic dysfunction (and potentially related gastrointestinal effects) in up to 52% of patients.^{44,45} With an intermediate dissolution and absorption profile (complete in 8-12 hours), extended-release niacin has a better balanced hepatic metabolism across the conjugative and amidative pathways.^{19,41}

TOLERANCE

Although flushing typically occurs as levels of circulating niacin increase, long-term tolerance to flushing results not from decreased niacin levels per se but rather from reduced output of PGD₂ over time with continued dosing.⁴⁶

TYPICAL CLINICAL PRESENTATION OF NIACIN FLUSHING

Virtually all niacin users initially experience flushing,¹⁹ typically commencing 15 to 30 minutes after ingesting immediate-release niacin, 30 to 120 minutes after ingesting extended-release niacin, or at more variable times after sustained-release niacin ingestion. Niacin users often experience “prickly heat” or a sense of warmth in the face, neck, ears, trunk, and, less frequently, the upper or lower extremities.⁴⁷ Other common features include erythema, itching, and tingling. Symptoms typically last for less than 1 hour to 2.5 hours.^{48,49} A meta-analysis demonstrated that the overall incidence of flushing with extended-release niacin was similar in women (79%) and men (82%), but women were significantly less likely to complete extended-release niacin studies (68% vs 79%; $P=.014$) and spent significantly less time using these medications (mean, 15.5 vs 17.3 weeks; $P<.001$).⁵⁰

ASSESSMENT

FLUSHING ASSESSMENT TOOL

A self-administered questionnaire with up to 22 items, the Flushing Assessment Tool evaluates the severity and troublesomeness of cutaneous warmth, redness, itching, and/or tingling. Individual and overall symptoms are rated on a

scale of 1 to 10, in which 1 through 3 signify mild flushing and 10 indicates very severe flushing.⁵¹ An 8-week validation trial was conducted in 276 adults with dyslipidemia.⁵¹ The overall troublesomeness of flushing was significantly correlated with treatment dissatisfaction. However, changes in most Flushing Assessment Tool measures from treatment week 1 to 6 suggested minimal effects of flushing on quality of life.⁵¹

FLUSHING SYMPTOM QUESTIONNAIRE

The Flushing Symptom Questionnaire comprises 11 items, each of which is scored as 0 (no symptom) to 10 (extreme symptoms). Item 3 concerning the severity of overall flushing symptoms is also termed the Global Flushing Severity Score. A similar 8-week RCT involving 175 candidates for niacin therapy was conducted to determine the validity of the Flushing Symptom Questionnaire.^{52,53} During the first niacin treatment week, 47% to 58% of patients experienced daily flushing episodes, most of which were mild and minimally bothersome, and 16% had sleep disturbances. In all, 43% to 49% of those taking 1.0 g of niacin had moderate or greater mean flushing (severity score of ≥ 4) compared with less than 15% of placebo recipients.⁵² The mean proportion of days with moderate or greater flushing decreased from 34% in treatment week 1 to 18% at week 2 or afterward.⁵³ Fourteen extended-release niacin users (8%) discontinued treatment because of flushing, including 11 (79%) in the first treatment week.

FREQUENCIES OF FLUSHING AND RELATED DISCONTINUATIONS WITH NIACIN-CONTAINING REGIMENS

LANDMARK TRIALS

Most of these studies evaluated the effects of immediate-release niacin, which in some cases was combined with bile acid resins and/or diet, on clinical, angiographic, and/or imaging end points (Table 1).^{5-10,12,15} In these studies, flushing was reported by up to 92% of patients receiving niacin-containing regimens but caused treatment discontinuation in smaller proportions (2.5%-10%).

OTHER CLINICAL TRIALS INVOLVING

NIACIN-CONTAINING REGIMENS: 2000-2009

Studies summarized in Table 2⁵⁴⁻⁶⁴ evaluated the effects of a combination regimen of extended-release niacin and a statin as well as of other combination regimens on surrogate (lipid or lipoprotein) outcome measures. These studies demonstrated that many patients (29%-74%) in these trials experienced at least 1 flushing episode, 75% to 92% of episodes were rated as mild or moderate, flushing frequencies declined over time, and approximately 4% to 12% of pa-

TABLE 2. Tolerability Findings From Smaller and Shorter-Term Clinical Trials of Niacin-Containing Therapies, 2000-2009^{a,b}

| Reference ^c | Population/design/ follow-up (wk) | Treatment (No. of patients randomized) | Measures to increase niacin adherence | Niacin vs placebo or other comparator (%) | | |
|----------------------------|--|--|---|--|---|--|
| | | | | Frequency of flushing (ever) | Discontinuation due to flushing | Adherence |
| SUPREME ⁵⁴ | ≥21 y with dyslipidemia/ RCOLT/12 | ER niacin/SA, 1.0/40 (wk 1-4) to 2.0/40 (wk 5-12) (119), and AT, 40 (80) | Dose at bedtime with low-fat snack; non-enteric-coated ASA, 325 mg, or NSAID 30 min before niacin dosing; avoid alcohol, hot beverages, and spicy foods; adhere to diet/TLC to qualify | 68 vs 10 ($P<.001$) (75 mild-moderate in ER niacin/ SA group) | 12 vs 0 ($P<.001$) | 92 vs 97 |
| SEACOAST II ⁵⁵ | ≥21 y with non-HDL-C levels greater than NCEP ATP III targets/ RDBCT/24 | ER niacin/SA, 0.5/40 (wk 1-4) to 1.0/40 (wk 5-24) (118); ER niacin/SA, 0.5/40 (wk 1-4) to 1.0/40 (wk 5-8) to 1.5/40 (wk 9-12) to 2.0/40 (wk 13-24) (102); SA 80 and ER niacin placebo (0.05 IR niacin) (123) | Dose at bedtime with low-fat snack; noncoated ASA (325 mg), IBU (200 mg), or other NSAID 30 min before niacin dosing; adhere to diet to qualify | 57 (1.0/40) to 67 (2.0/40) vs 50 (SA); serious flush: 4 (1.0/40 mg) to 6 (2.0/40) vs 3 (SA/ER niacin placebo); mild- moderate flush: 78 (ER niacin /SA) vs 91 (SA/ER niacin placebo) | 4 (1.0/40) to 5 (2.0/40) vs 0.8 (SA and ER niacin placebo) | 98 in all groups |
| SEACOAST I ⁵⁶ | Same as for SEACOAST II (see above) | ER niacin/SA, 0.5/20 to 1.0/20 (127); ER niacin/SA, 0.5/20 to 2.0/20 (66); ER niacin titrated as in SEACOAST II); SA 20 and ER niacin placebo (0.05 IR niacin) (121) | Dose at bedtime with low-fat snack; ASA, 325 mg, or NSAID (IBU, 200 mg) 30 min before niacin dosing; adhere to diet to qualify | 54 (1.0/20) to 60 (2.0/20) vs 45 (SA/ER niacin placebo); serious flush: 7 (1.0/20) to 11 (2.0/20) vs 0 ($P<.05$) ^d | 7 (1.0/20) to 11 (2.0/20) vs 0 ^d | 96 (2.0/20) to 97 (1.0/ 20) vs 99 (SA 20/ER niacin placebo) |
| OCEANS ⁵⁷ | Same as for SEACOAST (see above)/ ROLT/24-52 | ER niacin/SA, 0.5/40 to 2/40 during 8 wk (258) or 12 wk (262) | Dose at bedtime with low-fat snack; ASA, 325 mg, IBU, or other NSAID 30 min before niacin dosing; adhere to qualify; 8- to 12-wk titration and back-titrate if suboptimal toleration | 74 (8 wk) vs 68 (12 wk; $P=NS$); serious flush: 6.7 (8 wk) vs 7.4 (12 wk) ^d | 6.7 (8 wk) vs 7.4 (12 wk) ^d | 82 (similar in each group) |
| Guyton et al ⁵⁸ | 18-79 y with type IIa/IIb hyper- lipidemia/ RDBCT/24 | EZ/SA, 10/20 (272); EZ/SA, 10/20, and ER niacin, 0.5-2.0, during 12 wk (676); ER niacin (as above) (272) | Dose at bedtime with low-fat snack; ASA, 325 mg, or NSAID (IBU, 200 mg) 30 min before niacin dosing; avoid hot drinks and alcohol | NA | 0.4 (EZ/SA) vs 10 (EZ/SA and ER niacin) vs 12 (ER niacin); $P<.001$ | NA |
| COMPELL ⁵⁹ | ≥21 y with LDL-C level greater than NCEP ATP III targets/ RCOLT/12 | ER niacin/AT, 0.5/20 to 2.0/40 (1-12 wk) (60); EZ/ SA, 10/20 to 10/40 (72) ^e | Dose at bedtime; remainder of dosage information NR in "Methods" section (55% in ER niacin groups used ASA) | NA | Approximately 20-25 (ER niacin/statin) vs 10 (EZ/SA) | 85 (ER niacin/ AT) vs 99 (EZ/SA) |
| Insull et al ⁶⁰ | ≥21 y with type IIa/IIb hyper- lipidemia/ RDBCT factorial/26 | ER niacin, 0.5-2.5, during 16 wk (31), plus LO, 10 (34), or plus LO, 20 (34), or plus LO, 40 (32), or LO, 10-40, monotherapy (33) | Dose at bedtime with snack; ASA, 325 mg ≤30 min before niacin dosing | 62 vs 15 (ER niacin vs LO) | 6 (ER niacin/LO) vs 10 (ER niacin) | NA |
| Capuzzi ^{61,62} | ≥18 y with combined dyslipidemia (type IIb/IV hyperlipidemia)/ RCOLT/24 | ER niacin/RO, 0.5-2.0/10 (80); ER niacin/RO, 0.5-1.0/10-40 (72); ER niacin, 0.5-2.0 (72); RO, 10-40 (46) | Dose at bedtime with low-fat snack; 18-wk dose escalation | 29-43 vs 0 (ER niacin regimens vs RO) | NA | NA |

(continued on page 370)

TABLE 2. Continued^{a,b}

| Reference ^c | Population/design/ follow-up (wk) | Treatment (No. of patients randomized) | Measures to increase niacin adherence | Niacin vs placebo or other comparator (%) | | |
|-----------------------------|---|---|---|---|---|--|
| | | | | Frequency of flushing (ever) | Discontinuation due to flushing | Adherence |
| ADVOCATE ⁶³ | 18-70 y with LDL-C level greater than targets and low NCEP ATP III HDL-C level/ RCOLT/16 | ER niacin/LO, 0.5/20 to 1.0/40 (79); ER niacin/ LO, 0.5-2.0/40 (78); SA, 10-40 (76) | Dose at bedtime with low-fat snack; ASA, 325 mg, or NSAID 30 min before niacin dosing; tolerate ER niacin and LO titration and adhere to diet to qualify; 16-wk ER niacin escalation | NA | 5 (1.0/40) to 8 (2.0/40) vs NR for SA | 94 (2.0/40) to 97 (1.0/40) vs 96 (SA) |
| Kashyap et al ⁶⁴ | ≥21 y with LDL-C level greater than NCEP ATP II targets/ROLT/52 | ER niacin/LO, 0.5/10 to 2/40, during 16 wk (814) | Dose at bedtime with low-fat snack; ASA 30 min before niacin dosing; down-titration permitted | NA | 10 | NA |

^a ADVOCATE = Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation; ASA = aspirin; AT = atorvastatin; COMPELL = Comparative Effects on Lipid Levels of Combination Therapy With a Statin and Extended-Release Niacin or Ezetimibe Versus a Statin Alone; ER = extended-release; EZ = ezetimibe; HDL-C = high-density lipoprotein cholesterol; IBU = ibuprofen; IR = immediate release; LDL-C = low-density lipoprotein cholesterol; LO = lovastatin; NA = not available; NCEP-ATP = National Cholesterol Education Program Adult Treatment Panel; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; OCEANS = Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin Extended-Release and Simvastatin in Patients with Dyslipidemia; RCOLT = randomized, controlled, open-label trial; RDBCT = randomized, double-blind controlled trial; RO = rosuvastatin; ROLT = randomized open-label trial; SA = simvastatin; SEACOAST = Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients With Dyslipidemia; SUPREME = Study to Compare the Lipid Effects of Niacin Extended-release and Simvastatin to Atorvastatin in Subjects with Hyperlipidemia or Mixed Dyslipidemia; TG = triglyceride; TLC = therapeutic lifestyle counseling.

^b Doses for statins are provided in milligrams and those for niacin are provided in grams, unless otherwise indicated.

^c Study reports are presented in descending order of date published and, within the same year, by descending number randomized value and/or study quality. Only prospective, randomized, controlled, interventional studies (or open-label extensions of such trials) with both efficacy and safety/tolerability data for 100 or more participants completing the study are included. Comparisons denote active treatment vs placebo, usual care, or statin monotherapy except where noted.

^d Flushing that was serious or led to discontinuation.

^e All medications in study not included.

tients discontinued treatment because of flushing.⁵⁴⁻⁶⁰ The long-term OCEANS (Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin Extended-Release and Simvastatin in Patients with Dyslipidemia) study showed that less than 40% of patients who experienced flushing in the first 12 weeks of treatment, when extended-release niacin/simvastatin doses were being escalated from 0.5 g/40 mg to 2.0 g/40 mg, did so during the following 12 weeks.⁵⁷

In the SEACOAST (Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients With Dyslipidemia) trial, 27% of patients who experienced flushing while taking 1.0 g/20 mg of extended-release niacin/simvastatin (and 30% of patients taking 2.0 g/20 mg of extended-release niacin/simvastatin) during the first 12 weeks but who completed the study did not flush during the second 12 weeks.⁵⁶ In the recent SUPREME (Study to Compare the Lipid Effects of Niacin Extended-Release and Simvastatin to Atorvastatin in Subjects With Hyperlipidemia or Mixed Dyslipidemia) trial, extended-release niacin was up-titrated more aggressively, from 1.0 g for treatment weeks 1 to 4 to 2.0 g for weeks 5 to 12⁵⁴; despite this, approximately 47% of patients experienced no flushing during weeks 1 to 4, 55% experienced no flushing during weeks 5 to 8, and 70% experienced no flushing during weeks 9 to 12 (Figure 2).⁵⁴ The overall incidence of flushing was approximately 39% during treatment week 1 and 26% at week 5 (when the dose was advanced).

CLINICAL TRIALS OF NIACIN MONOTHERAPY: 1985-1999

Studies summarized in eTable 1⁶⁵⁻⁷³ (available online, linked to this article) evaluated the effects of niacin monotherapy on surrogate (lipid or lipoprotein) end points and patient-related flushing per se (ie, flush provocation studies). In 1 long-term study, more than 40% of patients using extended-release niacin experienced flushing at treatment week 4 compared with less than 20% at week 96.⁶⁵ The mean per-patient incidence of flushing per month decreased approximately 10-fold: from 1.9 episodes to 0.19 episode.

In a meta-analysis⁷⁴ of HDL-C-raising therapies involving more than 4000 patients using immediate-release niacin (n=3062),⁷⁵⁻⁸³ sustained-release niacin (n=536),^{66,67,77,84-86} or extended-release niacin (n=648),^{68-71,87,88} some of the results of which are summarized in eTable 1, most patients (70%) receiving niacin experienced flushing (vs 4% with placebo; $P<.001$). This proportion included 85% of patients receiving immediate-release niacin, 66% receiving extended-release niacin, and 26% receiving sustained-release niacin.⁷⁴ Approximately 13% of niacin users discontinued treatment (vs 6% of those receiving a placebo).

Extended- or Prolonged-Release Niacin. Eleven additional published reports provided data on flushing in more than 7000 patients.⁸⁹⁻⁹⁹ A particularly low frequency of flushing was observed in the IMPACT (Impact of Medical Specialty on Patient Compliance to Treatment) study, a 12-week, open-label trial involving 4499 patients with dyslipidemia

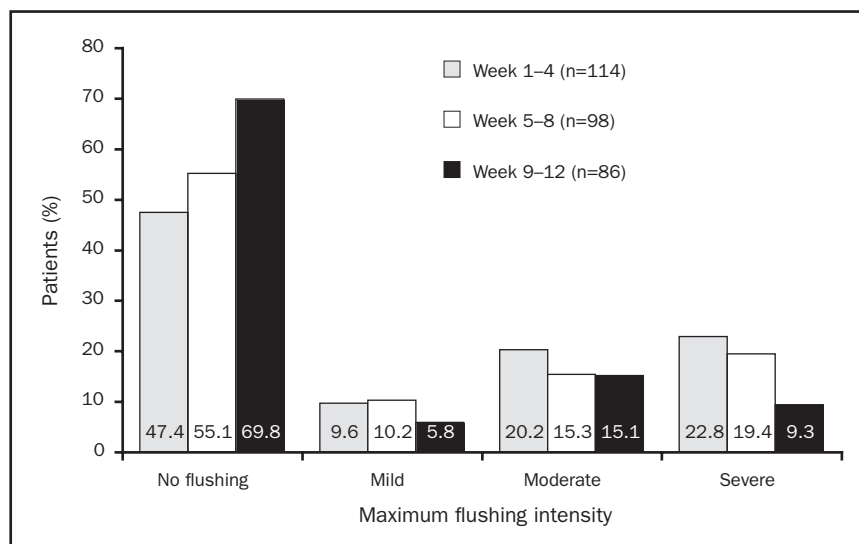


FIGURE 2. Decrease in the proportion of patients receiving extended-release niacin/simvastatin who experienced flushing and decrease in flushing intensity with increased duration of treatment in the Study to Compare the Lipid Effects of Niacin Extended-Release and Simvastatin to Atorvastatin in Subjects With Hyperlipidemia or Mixed Dyslipidemia (SUPREME). Bars depict maximum intensity of flushing experienced in each 4-wk period. No increase in flushing intensity was observed during weeks 5 to 8, when the daily dose of extended-release niacin/simvastatin was increased from 1 g/40 mg to 2 g/40 mg. From *J Clin Lipidol*,⁵⁴ with permission from Elsevier.

receiving combination therapy with extended-release niacin and lovastatin (0.5 g/20 mg to 1.0 g/40 mg) once nightly.⁹⁰ Before beginning therapy, patients received a recorded message about controlling cholesterol, dietary and physical activity counseling, and extended-release niacin's safety profile, with a focus on flushing. Patients also received written reminders to take their medications. At treatment week 8, patients were reevaluated, with laboratory monitoring, queries about adverse events, and adherence reminders, including dosing at bedtime with a low-fat snack and taking aspirin or an NSAID 30 minutes before niacin dosing. Only 18% of extended-release niacin users reported daily flushing, and 6% of patients discontinued niacin because of flushing.

Sustained-Release Niacin. Three prospective trials^{44,100,101} and 2 retrospective studies^{102,103} of patients receiving sustained-release niacin were identified. In a study by McKenney et al,⁴⁴ higher proportions of patients receiving immediate-release niacin (22%-53%) than sustained-release niacin (13%-22%) at daily doses of 0.25 to 3.0 g experienced vasodilator symptoms. In the other prospective studies, 0% to approximately 7% of patients discontinued use of sustained-release niacin because of flushing.^{100,101} Other studies did not report flushing data specifically by niacin formulation and were excluded.¹⁰⁴⁻¹⁰⁷

Immediate-Release Niacin. Nine smaller studies assessed the effects of immediate-release niacin, alone or in combination, on more than 600 patients receiving immediate-release

niacin-containing regimens in prospective¹⁰⁸⁻¹¹⁵ and retrospective¹¹⁶ studies. Many involved high starting doses of immediate-release niacin or rapid titration schedules. The percentage of patients discontinuing use of immediate-release niacin because of flushing ranged from 0% to 21%. Other studies without specific flushing data were excluded.^{104,117-119}

STRATEGIES TO PREVENT OR MANAGE NIACIN FLUSHING

COUNSELING

According to the Health Belief Model,¹²⁰⁻¹²³ patients are more likely to adhere to their treatments if they understand that they are susceptible to a disease, that treatment will reduce this susceptibility (without causing offsetting untoward effects), and if they are personally able to adopt the treatment. Given that dyslipidemia is a largely asymptomatic condition, it can be difficult to persuade a patient with no observable symptoms to take a medication that initially causes discomfort. Accordingly, it is important to explain the potential benefits of niacin therapy; the typically transitory, reversible, and harmless nature of flushing; and, in contrast, the stable and lasting coronary preventive benefits of continued niacin administration (Table 3). Patients need to know that niacin for dyslipidemia is essentially a "lifetime drug."

Engaging the patient in this sort of dialogue can help to cement a stronger physician-patient bond. Patients are ad-

TABLE 3. Educational Messages to Help Patients Prevent or Minimize Niacin Flushing

Why has your doctor prescribed treatment with niacin (or a niacin-containing treatment)?

You have had a heart attack, stroke, or other disease of your blood vessels (arteries)

You have a pattern of blood lipids (dyslipidemia) that can cause a serious disease of your arteries (atherosclerosis) and increase your risk of having a heart attack or stroke. This includes low levels of HDL (good) cholesterol

You may feel fine. However, you are still at higher risk and need to take your niacin to prevent a heart attack or stroke

What is niacin flushing?

It is a feeling of warmth or "prickly heat" with redness, usually in your face or torso; itching; and/or tingling. It is harmless

Scientists think that it is caused when niacin dilates small blood vessels in your skin (capillaries)

Many people who use niacin for the first time experience flushing within about 2 h, and it usually lasts for 1-3 h

Niacin flushing may be uncomfortable or even disrupt your sleep but usually does not reduce quality of life

Many niacin users flush less often and/or less severely over time (especially after the first week or two) while taking the drug

Why is it important to try your best to keep taking your niacin despite flushing?

Unlike flushing, which usually passes in 1-3 h, the benefits of niacin are permanent (if you keep taking it)

Within weeks of taking your niacin, the health of your arteries should improve

Within months, your atherosclerosis may stop progressing (or even reverse), and you can prevent a heart attack or stroke

Within years, you can prevent a heart attack, stroke, or other causes of death

Every time you increase your niacin dose by 500 mg (0.5 g) up to about 2000 mg (2.0 g), you can raise your HDL (good) cholesterol (by 8%) and lower your LDL (bad) cholesterol (by 4%)

What can you do to prevent or reduce niacin flushing (besides discussing it with your physician)?

Take an aspirin or NSAID 30 min before taking your niacin, with it, or shortly thereafter

Take your niacin with a low-fat snack (eg, applesauce, piece of fruit, low-fat yogurt). This may also help to increase the amount of niacin your body absorbs and avoid having a stomachache or other digestive symptoms after taking it

Avoid eating spicy foods, drinking hot beverages or alcohol, and taking hot showers or baths after taking your niacin

Try not to miss doses of your niacin. If you do, your doctor may advise you to restart your medicine at a lower dose (eg, the dose you originally started with) and take an aspirin or NSAID as you did when initially using the medication

This information is being provided to you by your physician to help you learn about niacin flushing but is not intended as a substitute for discussion with him or her. HDL = high-density lipoprotein; LDL = low-density lipoprotein; NSAID = nonsteroidal anti-inflammatory drug (eg, ibuprofen).

vised to take niacin with a low-fat snack (eg, applesauce) at bedtime or with a meal, which can improve both vasocutaneous and gastrointestinal tolerability. Taking niacin with food may also increase niacin's bioavailability,¹²⁴ whereas taking it at bedtime allows many patients to sleep through any flushing and may blunt nocturnal release of free fatty acids.

Counseling approaches recommended by the National Lipid Association to prevent or minimize flushing are pre-

sented in Table 4.¹²⁵ As suggested by the IMPACT study,⁹⁰ ongoing patient education and reminders may assist in promoting niacin adherence. Patients are asked to describe the symptoms of flushing by formulation; for instance, flushing with immediate-release niacin is probably the shortest lived and may be a more consistent experience compared with other formulations.¹²⁶ Immediate-release niacin should be administered in divided doses, typically in the middle of breakfast and dinner, and after taking 325 mg of aspirin on awakening (at least during the early weeks of treatment).¹²⁶ One approach is to initiate immediate-release niacin treatment at 0.05 to 0.10 g (50-100 mg) twice daily for the first week, then double the daily dose each week until the daily dosage is raised to 1.0 to 2.0 g.¹²⁷

Patients should be advised that flushing is a nonallergic, typically time-limited phenomenon; although uncomfortable, it is not usually harmful. Flushing will not occur with each dose and should subside during a period of weeks if not days with continued dosing. Failure of flushing to abate with time may reflect inconsistent dosing. If the patient has not taken niacin in 3 or more days, it may be necessary to restart treatment at a low dose and reescalate. To improve patient expectations of flushing, it may be useful to administer the starting niacin dose in the office. In a number of clinical trials, patients took either 325 mg of a non-enteric-coated aspirin or an NSAID (eg, 200 mg of ibuprofen) 30 to 60 minutes before (but not 15 or 120 minutes before) niacin use, and this approach has been endorsed by the National Lipid Association.¹²⁵ Some authorities recommend taking 325 mg of aspirin the day before the first niacin dose and continuing its use for the first month of treatment.¹²⁶ Given the perception of heat associated with flushing, patients may wish to take their niacin with a cold (non-alcoholic) beverage. They should avoid alcohol, spicy foods, hot beverages, and hot showers or baths around the time of dosing. Patients should also be advised to avoid missing niacin doses and to report any such lapses to their clinicians.

In contrast to certain RCTs that did not allow back-titration (down-titration), the physician and patient have wide latitude to individualize the schedule of niacin dose escalation. Some sensitive patients will need to "start lower and go slower" or even "start low, go slow, and go back." To assist in this process, it is important to schedule a follow-up visit with laboratory monitoring approximately 4 to 8 weeks after initiating niacin treatment and to identify other patient concerns about flushing. Doing so enables the physician to assess patient safety and toleration of niacin, make any needed medication adjustments, and review key counseling messages. The follow-up visit also offers an occasion to revisit the lipid and coronary preventive benefits of niacin, focus patients on attainable intermediate

TABLE 4. Educational Messages to Help Physicians Prevent or Minimize Niacin Flushing and Enhance Tolerability

1. Long-term adherence to niacin is dependent on patient awareness and education. Patients should be advised that flushing is typically a time-limited adverse event and that long-term adherence is necessary to reduce cardiovascular risk
2. Describe the flush to the patient before first use. If time permits, consider administering a small dose of niacin in the office so that the patient knows what to expect. Extended-release niacin has achieved greater patient acceptance with regard to flushing compared with immediate-release niacin. The flush can be described as a "prickly heat" feeling, usually concentrated in the head, neck, and shoulders. It usually occurs 15-30 min after ingesting immediate-release niacin, 30-120 min after ingesting extended-release niacin, or at highly variable times after ingesting slow-release niacin. Flushing episodes usually last 5-180 min. Treatment with immediate-release niacin is associated with a shorter duration of flushing than longer-acting formulations
3. Flushing is a nonallergic phenomenon confined largely to the skin. Though uncomfortable, it is not associated with any permanent harm. Patients often tolerate minor skin discomfort of short duration, even when it occurs repeatedly, if they understand that it is an expected accompaniment of treatment without the serious implications of an allergic drug reaction
4. "Go low and slow": niacin therapy should begin with low doses (eg, 0.125-0.250 g twice daily or 0.5 g of extended-release niacin with a low-fat snack at bedtime), with gradual increases during a period of weeks to months. Flushing generally occurs when a threshold dose of niacin is administered, in the range of 0.25-1.0 g
5. The frequency and intensity of flushing can be reduced by taking aspirin (325 mg), ibuprofen (200 mg), or another NSAID 30-60 min before niacin ingestion. Aspirin (81 mg) may not provide sufficient inhibition of prostaglandin synthesis to inhibit flushing. In long-term use, it is best to limit aspirin or NSAID pretreatment to no more than 1-2 times per day if multiple daily doses of niacin are used. Because flushing frequency decreases over weeks or months, the patient may choose to take aspirin concomitantly with niacin for the sake of convenience
6. To minimize flushing, regular niacin (ie, immediate-release niacin, crystalline niacin), usually administered twice daily with breakfast and supper, is best taken in the middle of the meal rather than just before or just after the meal. Slow-release niacin is administered twice daily with meals
7. Inositol hexanicotinate (hexaniacinatate) is sold over the counter as "no-flush" or "flush-free" niacin. However, the niacin appears not to be bioavailable and should not be used: the compound has never been shown to release free niacin, raise circulating niacin levels, or improve plasma lipid levels
8. Flushing with extended-release niacin is minimized by taking it at bedtime. Taking extended-release niacin with a small, low-fat snack such as whole-wheat crackers or skim milk also helps to reduce flushing
9. Flushing does not occur after every dose of niacin. In clinical trials, the median number of flushing episodes was 5 during the first 8 wk after initiating treatment with extended-release niacin
10. Failure of flushing rates to decrease, or reappearance of flushing, may be due to inconsistent dosing. A niacin-free interval of ≥ 3 d will often necessitate retitration to avoid substantial flushing
11. The niacin flush differs from a menopausal hot flash in that the former is generally not accompanied by sweating
12. Alcohol, spicy foods, hot beverages, and hot baths or showers all can exacerbate flushing and may need to be timed sufficiently before or after niacin dosing
13. Some specialists suggest that occasional prolonged or intense flushing might be shortened by chewing an aspirin tablet to give buccal absorption of aspirin

NSAID = nonsteroidal anti-inflammatory drug.

Adapted from *Am J Cardiol*,¹²⁵ with permission from Elsevier.

objectives (eg, achievement of cholesterol level goals), and hence promote adherence.¹²⁸

PHARMACOTHERAPEUTIC STRATEGIES

Optimized Niacin Formulation. Extended-release niacin was reformulated with a different coating to optimize its dissolution, absorption, and metabolic profiles. In a flush provocation study, 53% of patients receiving 650 mg of aspirin before treatment and 61% receiving 650 mg of concomitant aspirin experienced flushing with 2.0 g of reformulated extended-release niacin.¹²⁹ Aspirin before treatment reduced the median duration of the first flush by approximately 43% (37 vs 65 minutes for extended-release niacin alone; $P=.008$), the mean intensity by 34% ($P<.001$), and the proportion of patients with moderate or greater flushing by 62% (14% vs 37%; $P<.001$).

Aspirin and NSAIDs. Findings from studies specifically evaluating adjunctive or prophylactic aspirin or NSAIDs to attenuate niacin flushing are summarized in eTable 2 (available online, linked to this article).¹²⁹⁻¹³⁴ Of note, 325 mg of aspirin significantly ($P<.001$ vs placebo) attenuated flushing symptoms when administered 30 to 60 but not 15 or 120 minutes before immediate-release niacin, and an aspirin dose of 650 mg was not superior to 325 mg.¹³² In another study, pretreatment with 325 mg of aspirin 30 minutes before niacin was significantly superior to 200 mg of ibuprofen in blunting flushing and itching in patients experiencing these manifestations.¹³³ In a previous study, 325 mg of aspirin was superior to 80 mg of aspirin in mitigating flushing with 0.5 g of immediate-release niacin.¹³⁴

The flushing-specific discontinuation rate in a recent 4-week study was 1.8% among patients randomized to receive 325 mg of aspirin before extended-release niacin treatment compared with 9.4% among those receiving extended-release niacin without aspirin ($P=.007$).¹³⁰ In this study, 15% of patients receiving aspirin prophylaxis with a 0.5- or 1.0-g starting dose of extended-release niacin experienced moderate or greater flushing during the first treatment week (vs 29% not receiving aspirin; $P=.01$). Pretreatment with aspirin significantly reduced mean maximum flushing severity, number of moderate or greater flushing episodes, and the incidence of flushing by 18% ($P=.014$; Figure 3).¹³⁰ The incidence of flushing was also significantly lower among patients receiving an extended-release niacin starting dose of 0.5 g (32%) compared with 1.0 g (53%; $P=.05$).

A literature review¹³⁵ demonstrated that the mean rate of treatment discontinuation because of niacin flushing was approximately 6.5% in studies in which 325 mg of aspirin was recommended as needed or mandatory to prevent or minimize flushing; 8% in studies using extended-

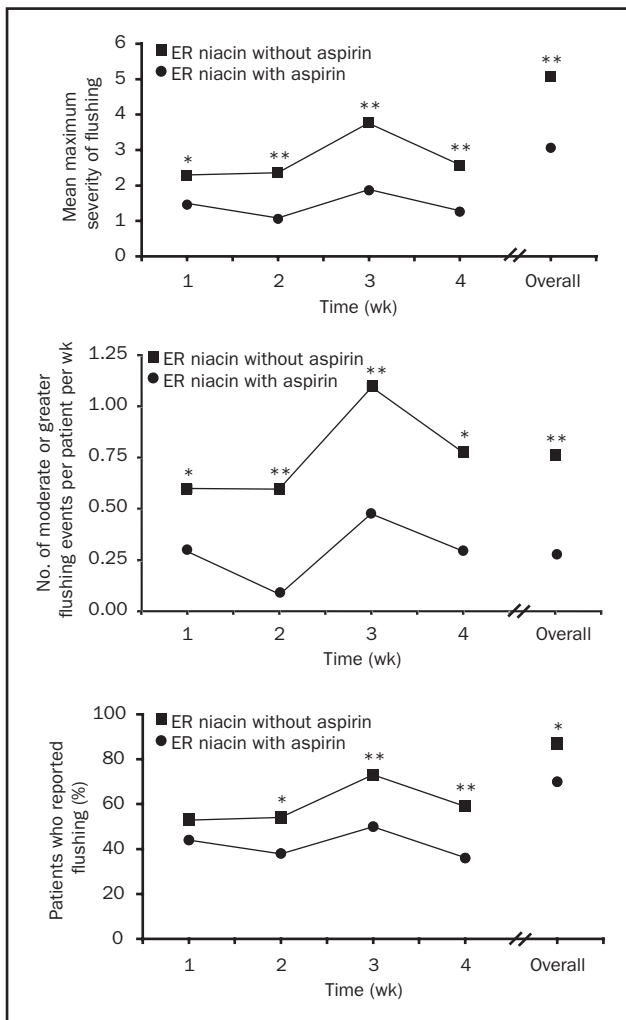


FIGURE 3. Severity of flushing events with and without aspirin (top and middle) and flushing incidence (bottom) in a study evaluating the effects of 1 wk of prophylaxis with 325 mg of aspirin, followed by ongoing treatment as an adjunct for flushing associated with extended-release niacin, 0.5 to 2.0 g, during treatment weeks 1 through 4. Top and Middle, Flushing events were graded on a 10-point scale ranging from mild (1-3) to very severe (10). Top, Mean maximum flushing severity scores are presented over time among patients who received aspirin treatment at any time (arms 1, 2, 4, and 5) vs patients who did not receive aspirin treatment (arms 3 and 6). Middle, The number of moderate or greater flushing events recorded per patient per week are presented over time among patients receiving aspirin treatment at any time (arms 1, 2, 4, and 5) vs patients who did not receive aspirin treatment (arms 3 and 6). * $P<.05$; ** $P<.001$ vs extended-release niacin with aspirin. From *Am J Cardiovasc Drugs*,¹³⁰ with permission from Wolters Kluwer Health.

release niacin vs 18% in those using immediate-release niacin. The mean incidence of niacin flushing across the studies was 29% (range, 18%-100%). In a recent study, 23% of patients receiving extended-release niacin and aspirin experienced flushing during the first treatment

month compared with 32% of those without prior aspirin therapy ($P=.02$).⁸⁹

Laropiprant. A selective PGD_2 receptor (DP1) antagonist approved as a treatment adjunct to mitigate niacin flushing in certain non-US markets, laropiprant has been combined with extended-release niacin (modified- or prolonged-release niacin; Tredaptive; Merck, Whitehouse Station, NJ). The proprietary extended-release niacin formulation in Tredaptive is not identical to the proprietary formulation in Niaspan, Advicor, and Simcor.

In healthy volunteers, laropiprant is rapidly absorbed (median time to maximum drug concentration, 0.8-2.0 hours), with no effects of food on absorption, and the apparent terminal elimination half-life is 10 to 18 hours.¹³⁶

In a single-dose study, adjunctive (concomitant) laropiprant significantly reduced flushing associated with 1.5 g of extended-release niacin: by 47% for a 30-mg dose of laropiprant, by 67% for a 100-mg dose, and by 74% for a 300-mg dose.¹³⁷ Coadministration of extended-release niacin with either 30 mg or 100 mg of laropiprant decreased peak malar (cheek) skin blood flow (objective measure of vasodilation) by 50% and 70%, respectively. Reductions in patient-rated flushing correlated significantly with decreases in malar blood flow ($r=0.64-0.68$; $P<.001$).¹³⁷ In multiple-dose studies, 200 mg of adjunctive laropiprant reduced time-weighted average flushing scores by 65% (vs 1.5 g of extended-release niacin alone) on day 1 and by 52% on day 3.¹³⁷ In a phase 1 study (study 044), coadministration of 325 mg of aspirin did not confer significant incremental benefits in reducing the incidence and severity of residual flushing associated with 40 mg of laropiprant and 2.0 g of extended-release niacin.¹³⁸

In a phase 2, dose-ranging study, adjunctive laropiprant (18.75 to 150 mg [pooled]) resulted in lower proportions of patients reporting moderate or greater flushing during the first week of treatment with 1.0 g of extended-release niacin (vs 1.0 g of extended-release niacin alone).¹³⁹ In a pivotal phase 3 study (study 020), approximately 31% of patients who were using adjunctive laropiprant and extended-release niacin (1.0 g) experienced moderate or greater flushing during treatment week 1 compared with 56% receiving monotherapy with 1.0 g of extended-release niacin ($P<.001$) and 6% taking placebo.¹⁴⁰ Corresponding proportions of patients with severe or extreme flushing were 14% in the laropiprant and extended-release niacin group and 33% in the extended-release niacin group ($P<.001$).¹⁴⁰

During treatment weeks 2 to 24 in study 020, 14% of patients taking laropiprant and extended-release niacin experienced 1 day per week or more with moderate or greater flushing compared with 29% of those taking extended-release niacin monotherapy ($P<.001$) and approx-

imately 2% of those taking placebo.¹⁴⁰ During the maintenance phase, patients in the laropiprant and extended-release niacin group experienced approximately 1 day of moderate or greater flushing per patient-month compared with 1 day per patient-week in the extended-release niacin group. Commenting on these data, the authors contended that “tolerance to this level of flushing is incomplete during at least a 6-month period.”¹⁴¹ Ten percent of the extended-release niacin and laropiprant group discontinued treatment because of flushing compared with 22% of the extended-release niacin group ($P < .001$) and less than 1.0% of the placebo group. The combination of laropiprant and extended-release niacin is being evaluated in the ongoing phase 3 HPS2-THRIVE (Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events).

DISCUSSION

THE WAY FORWARD

One ongoing controversy concerns schedules for extended-release niacin dose escalation. For many years, the adage about niacin dosing has been to “start low and go slow[ly].” More recently, however, studies have suggested that a shorter titration interval, on the order of 8 or 12 weeks (vs 16 weeks), to increase the niacin daily dose from 0.5 to 2.0 g may be associated with comparable or even superior flushing data. In the OCEANS study, 68% of patients using an 8-week extended-release niacin and simvastatin titration schedule experienced flushing compared with approximately 74% of those using a 12-week titration.⁵⁷ Regimens of patients receiving the PGD₂ antagonist laropiprant along with extended-release niacin have consisted of a 2-step schedule: initiating niacin treatment at the relatively high daily dose of 1.0 g, which was maintained for 4 weeks, and then escalating to 2 g at treatment week 4 and maintaining this dose for 12 weeks.¹⁴² In my practice, we use a combination of these 2 approaches, starting low (0.5 g/d) and going slowly (for a total of 8 weeks) until a stable dose of 1.0 g has been reached. At this juncture, the daily niacin dose is increased directly from 1.0 g to the maintenance daily dose of 2.0 g (if tolerated).

Although neither aspirin nor laropiprant influences the lipid-modifying effects of niacin, neither agent completely abrogates the flushing response. Aspirin can also saturate the glycine elimination (conjugative) pathway shared with niacin and, hence, in theory, actually increase plasma niacin levels. This could, in turn, contribute to increased GPR109A receptor-mediated, PGD₂-driven flushing.^{134,143} However, this probably has never been observed because the net effect of 325 mg of aspirin is to reduce PGD₂ levels and hence contribute to the development of tachyphylaxis.¹³⁴

Furthermore, aspirin can increase the risk of gastrointestinal events and/or bleeding. Niacin is often associated with gastrointestinal effects, and both active peptic ulcer disease and arterial bleeding contraindicate treatment with niacin-containing regimens.³³⁻³⁵

In a clinical pharmacology study, laropiprant at supra-therapeutic doses had no significant effect on bleeding time, whereas 325 mg of aspirin prolonged bleeding time by 44% ($P = .004$ vs placebo) 24 hours after administration.¹³⁶ However, laropiprant also causes adverse gastrointestinal effects. In the pivotal laropiprant phase 3 study (study 020), 2.9% of the laropiprant and extended-release niacin group experienced nausea (vs 2.0% with extended-release niacin alone) and 2.6% experienced diarrhea (vs 1.8%).¹⁴⁰ Across laropiprant studies 020, 022, and 054, 16.5% of the laropiprant and extended-release niacin groups experienced gastrointestinal adverse events (vs 11.7% of the extended-release niacin group).¹⁴⁴

Despite a lower rate of discontinuation because of flushing in the laropiprant and extended-release niacin groups (approximately 4% vs 9% with extended-release niacin), a higher proportion of the laropiprant and extended-release niacin group discontinued treatment because of gastrointestinal (2.5% vs 1.5%) or laboratory adverse events (1.3% vs 0.7%), particularly abnormal liver function test results. In its Committee for Medicinal Products for Human Use assessment, the European Medicines Agency concluded that “the lower discontinuation rate due to flushing [with laropiprant and extended-release niacin vs extended-release niacin alone] is partly offset by other side effects, in particular the occurrence of gastrointestinal symptoms.”¹⁴⁴ In a recent study (reported after the literature search had been conducted), frequencies of gastrointestinal adverse events were comparable in patients randomized to laropiprant and extended-release niacin (1.0 g for 4 weeks followed by 2.0 g for 12 weeks) or extended-release niacin monotherapy (0.5 g titrated to 2.0 g at 0.5-g monthly increments) when data were normalized by time of exposure to extended-release niacin at 2.0 g (1.7% vs 1.8%).¹⁴² In this study, approximately 7% of patients in the laropiprant plus extended-release niacin group discontinued treatment because of flushing, compared with 12% in the extended-release niacin group ($P = .002$).¹⁴²

In contrast, patients receiving laropiprant and extended-release niacin may have increased frequencies of niacin-related, nonflushing adverse events (vs extended-release niacin monotherapy) because of dose inequities; recipients of laropiprant and extended-release niacin might experience a somewhat higher frequency of nonvasodilatory untoward effects because they are able to achieve higher niacin doses without flushing. Treatment adjuncts such as laropiprant and aspirin typically need to be used for a relatively

short period to tide patients over the early niacin dosing period, hence limiting overall exposure to these adjuncts. Given a low percentage of patients discontinuing laropiprant and extended-release niacin therapy after treatment week 16 and the dubious effects of long-term withdrawal of laropiprant on extended-release niacin flushing, the European Medicines Agency also concluded that the efficacy of laropiprant had not been demonstrated for more than 24 weeks.¹⁴⁴

Perhaps the most appropriate use of aspirin and laropiprant, along with counseling and other measures, should be as temporary “bridges” that are targeted to patients during the first several weeks of treatment, when niacin doses are being advanced, as well as when restarting niacin treatment after a lapse in dosing. Studies are needed to predict which patients are most likely to experience poor vasocutaneous toleration of niacin and target the most intensive counseling and pharmacological support to these individuals. However, no study to my knowledge has yet demonstrated an “at-risk genotype” for flushing. Studies are also needed to compare the effects of aspirin prophylaxis and adjunctive laropiprant on flushing, as well as to establish an optimal dosing paradigm (eg, via studies comparing extended-release niacin dosing with dinner or at bedtime).

Other potential treatment adjuncts to mitigate niacin flushing include agents targeting the serotonergic component of the vasocutaneous reaction (eg, cyproheptadine [off-label indication]). Other candidates include flavonoids (eg, quercetin [Algonot Plus; Algonot LLC, Sarasota, FL] and luteolin [Luti-Max; SYNORx Inc, San Clemente, CA]), which also inhibit mast cell PGD₂ secretion.^{145,146} Another possible approach is to develop new niacin receptor (GPR109A) agonists with a superior therapeutic index for inhibiting lipolysis (and hence improving lipid levels) over vasodilation, even though both of these processes are receptor-mediated.¹⁴⁷

POTENTIAL LIMITATIONS

Limitations of this review include potential publication bias; the decision not to include case reports and case series; a focus on data from RCTs, in which patients are often highly selected for superior treatment adherence (potential selection bias); and inclusion of healthy volunteers in some of the studies. Many studies reviewed reported frequencies of flushing separately from those of the individual symptoms (eg, pruritus [itching] or paresthesia [tingling]). These factors may have caused an underestimation of the true incidence and severity of flushing associated with niacin compared with more naturalistic clinical settings.

Many RCTs in this review did not determine whether decreases in mean incidences of flushing over time with niacin truly resulted from tachyphylaxis in most patients

or from a survivor effect in which patients with poor toleration were more likely to discontinue treatment in the early weeks, leaving a more flushing-resistant phenotype in the later weeks. In future trials, conducting an analysis of “time to first flush” or “time [or cumulative niacin dose] to flushing-related discontinuation” might help to adjust for this potential statistical artifact.^{142,148,149}

Data on available niacin receptor agonists (Acipimox [Pfizer]) or from proprietary databases (eg, EMBASE) were not reviewed. Many reports providing data on flushing did not explicitly state whether the aspirin administered was enteric-coated. Combined with cellulose and/or other inert ingredients that resist gastric disintegration, coated aspirin is absorbed more slowly than other forms, with a time to peak concentration of approximately 3 to 4 hours compared with 0.25 hour to 2 hours for uncoated aspirin, which is closer to the time at onset of flushing with many niacin formulations. Hence, coated aspirin may need to be administered more than 30 minutes before niacin, although no clinical study has evaluated the comparative antifleush efficacy of coated (vs uncoated) aspirin.¹⁵⁰

CONCLUSION

Niacin is the most effective agent for raising HDL-C levels, but its use has been constrained by potentially dose-limiting, receptor-mediated, mainly PG-driven cutaneous vasodilation with flushing. Although typically mild or moderate and reversible with continued dosing, niacin flushing warrants effective counseling, treatment adjuncts or prophylaxis, careful dose escalation with follow-up monitoring, input from the patient, and regimen adjustments as needed. Wider implementation of these measures should enable higher proportions of patients to reach and persist with sufficient niacin doses over time to prevent cardiovascular events.

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